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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GRASER, JENNIFER E	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,053	SU ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *1-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/8/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 12-28 and SEQ ID NO:14, in the reply filed on 6/19/07 is acknowledged. The traversal is on the ground(s) that the common special technical feature is the generic formula set forth in formula 1. This is not found persuasive because as stated in the Restriction requirement: 'The inventions of Groups I and II contain special technical features which are biologically, chemically and structurally different products. The polypeptide of group II and polynucleotide of group I are patentably distinct inventions for the following reasons. Polypeptides, which are composed of amino acids, and polynucleotides, which are composed of purine and pyrimidine units, are structurally distinct molecules. Formula 1 is not the special technical feature of the Groups. See the Restriction Requirement. Claims 1-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention

The requirement is still deemed proper and is therefore made **FINAL**.

Claim Objections

2. Claims 12-28 are objected to because of the following informalities: they contain non-elected subject matter which must be removed from the claims. Additionally, claim 12 should be written to incorporate the subject matter of the non-elected claim from which it depends. Appropriate correction is required.

Claim Rejections - 35 USC § 112-2nd paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 12-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is extremely vague and confusing because it recites 'a nucleic acid sequence encoding the fusion protein of (non-elected) claim 6, yet claim 6 recites an undefined formula with many different amino acids and varying sequence possibilities, present or absent. The nucleic acid sequence is not adequately defined. The formula is extremely vague and confusing and allows for many variations and a string of different sequence identifiers with a large number of different possibilities. Accordingly, the metes and bounds of the invention cannot be understood. A nucleic acid sequence should be defined by a single nucleic acid sequence as defined in a single sequence identification number, e.g., SEQ ID NO: X, or by the specific amino acid sequence it encodes, e.g, SEQ ID NO: 14. Claim 12 should also recite that the nucleic acid sequence is isolated and/or purified. Appropriate amendment and correction is required.

Claim 16 should recite the appropriate deposit identification numbers for the host cells, otherwise it is vague and indefinite what is encompassed by the names recited therein. The mere recitation of a name, i.e., JM101, to describe the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. The claim should provide the appropriate deposit/accession

number, which would allow for one to identify the protein without ambiguity. The mere recitation of a name does not adequately define the cell.

Claim 20 is vague and indefinite due to the term 'inducer'. Is this 'inducer' separate from the 'suitable conditions'? What is encompassed by an 'inducer'?

Claim 21 is vague and indefinite for the condition "temperature". What is encompassed by this term. What is the temperature? Is this a temperature appropriate/suitable for expression of the vector, etc.?

Claim Rejections - 35 USC § 112-Scope of Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "an isolated nucleic acid sequence which encodes an amino acid sequence as set forth in SEQ ID NO: 14 and expression vectors, host cells and methods of recombinant production comprising/using this sequence, does not reasonably provide enablement for a nucleic acid sequence encoding the fusion protein of claim 6 (or host cells and methods of recombinant production comprising/using this sequence). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The breadth of the instant claims is drawn to polynucleotides that are not specified in the sequence disclosure. The specification states that substitutions,

additions, or deletions may be made to the defined sequences; however, the specification provides no guidance as to what nucleic acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which nucleotides/amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. To start with the DNA sequence first, this requires even more work on the part of the skilled artisan.

The formula in non-elected claim 2 (from which the claim depends) recites that any amino acid may be in position X1, X2, X3 and X5, A6 –A9 may either be there or contain several different variations while T2 may be absent or a His-Tag or one or more petpidic cleaveage sites. This allows for a huge amount of variation. The instant claims are drawn to nucleic acids comprising a sequence with a variation from a nucleic acid which encodes a protein. Selective point mutation (or the presence of a any amino acid in certain positions) to one key residue could eliminate the function of the polypeptide. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding

interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. As stated above, Applicants have not shown which nucleotides may be changed without causing a detrimental effect to the protein in which it encodes. Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a single amino acid difference may account for markedly different biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is

granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Adequate enablement and written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Given the lack of guidance contained in the specification regarding acceptable nucleotide substitutions, additions or deletions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112-Written Description

7. Claims 12-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth an isolated nucleic acid sequence encoding an amino acid

sequence as set forth SEQ ID NO:14 and therefore the written description is not commensurate in scope with the claims.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of a nucleic acid sequence encoding SEQ ID NO:14, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel,

25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". No disclosure, beyond the mere mention of allelic variants is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated nucleic acid sequence which encodes an amino acid sequence as set forth in SEQ ID NO: 14, but not the full breadth of the claims meets the written description provisions of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112-Deposit Information

8. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the deposit of host cells DH5c~, BL21, JM101 or JM105 or NM522 or N99Cl+. Because it is not clear that the properties of these host cells are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of the host cells, a suitable deposit for patent purposes is required. Exact replication of the host cells is an unpredictable event.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of the deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required.

If the deposits have not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR

§1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become non-viable or non-replicable.

In addition, a deposit of the biological material that is capable of self-replication either directly or indirectly must be viable at the time of the deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1)The name and address of the depository;
2)The name and address of the depositor;
3)The date of deposit;
4)The identity of the deposit and the accession number given by the depository;
5)The date of the viability test;
6)The procedures used to obtain a sample if the test is not done by the depository; and
7)A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 12-17 and 19-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Kovacevic et al (US 4,977,089).

Kovacevic et al teach a that the nucleotide sequence for the staphylococcal nuclease gene has been known since 1983. See column 2, lines 51-55. in 1985, Kovacevic disclosed where the translation start of the gene was located. The reference teaches a nucleic sequence which is 100% identical to Applicant's SEQ ID NO: 14. See sequence alignment available in Public PAIR under the 'supplemental content' tab. Column 25 teaches the expression and secretion of proinsulin-nuclease proteins in E.coli cells. See column 26, lines 45-55 which teaches the use of E.coli host cells. Kovacevic specifically teach expression vectors operably linked to promoters throughout the entire disclosure and their expression in recombinant protein production methods. Column 28, lines 5-20 teach the release of the plasmid-encoded products by techniques well known in the art. Claim 2 (from which the claims depend) uses the open language 'having' which allows for the inclusion of additional nucleic acids, e.g., including use of the full-length sequence for S.aureus nuclease.

11. Claims 12-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Murray et al (US 6,365,~~437~~ 347).

JD 7/18/07

Murray et al teach the nucleic acid sequence of an S.aureus nuclease with a poly His tag. See Fig 2D-SEQ ID NO: 7. . The reference teaches a nucleic sequence which is 100% identical to Applicant's SEQ ID NO: 14. See sequence alignment available in Public PAIR under the 'supplemental content' tab. Murray teach the use of the S.aureus nuclease as a chimeric protein with inert carriers. They teach the recombinant expression of said fusion/chimeric proteins. See Column 2. Column 5, lines 27-44 teach that the carrier protein may be a derivative of staphyloccal nuclease, a small, heat

stable protein, which can be expressed intracellularly at high levels in both budding yeast and bacteria. It is taught that this carrier protein may be modified by the addition of an exogenous sequence that facilitates their isolation and purification, such as c-terminal polyhistidine sequences or n-terminal hemaglutinin tags. See column 5, lines 35-44. It is taught that E.coli may be used as a host cell, see bottom of column 12 for example. Purification procedures of the protein from medium are also taught. Claim 2 (from which the claims depend) uses the open language 'having' which allows for the inclusion of additional nucleic acids, e.g., including use of the full-length sequence for S.aureus nuclease.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Kovacevic et al (US 4,977,089).

The teachings of Kovacevic et al are set forth above. Although they do not particularly recite the purification/release methods recited in instant claims 23-28, by Kovacevic et al do teach Column 28, lines 5-20 teach the release of the plasmid-encoded products by any techniques well known in the art. The techniques outlined in claims 23-28 were notoriously well known in the prior art at the time the invention was

made and it would have been obvious for one of ordinary skill in the art to use any one of them to isolate the polypeptides.

Prior art cited, not relied on:

13. US Patent No. 5,834,233 abd WO95/10614 both teach isolated nucleic acid sequences which are 100% identical to Applicants' SEQ ID NO:14.

14. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

7/18/07

Jennifer Graser
Primary Examiner
Art Unit 1645